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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,450	05/04/2007	Malte Peters	DEBE:069US/10612950	5684

32425 7590 12/26/2008

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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
12/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,450	PETERS ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *10,11,13-16 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12 and 17-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/29/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The election without traverse filed October 14, 2008, is acknowledged and has been entered.

Applicant has elected the invention of Group V, claims 9 and 22, drawn to a method of treating colon cancer in a human patient by administering to said patient a human immunoglobulin specifically binding to the human EpCAM antigen, said immunoglobulin exhibiting a serum half-life of at least 15 days, said method comprising the step of administering said immunoglobulin no more frequently than once every week.

Claims 1-8, 12, 17-21 and 23-24 have been identified as linking claims in the restriction requirement and have also be examined with the claims to the elected invention (see MPEP 809).

2. Claims 1-25 are pending in the application. Claims 10-11, 13-16 and 25 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1-9, 12 and 17-24 are under examination.

Information Disclosure Statement

4. The references cited in the information disclosure statement filed on May 29, 2007, have been considered.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

In this case, the declaration page listing co-inventor Peters does not indicate that

there any additional declaration pages attached and the declaration page listing the other co-inventors does not indicate that it is an additional page, and therefore it cannot be known whether the declaration signed by each inventor contained a complete listing of all inventors. While each inventor need not execute the same oath or declaration, each oath or declaration executed by an inventor must contain a complete listing of all inventors so as to clearly indicate what each inventor believes to be the appropriate inventive entity. Where individual declarations are executed, they must be submitted as individual declarations rather than combined into one declaration. For example, where the inventive entity is A and B, a declaration may not be executed only by A naming only A as the inventor and a different declaration may not be executed only by B naming only B as the inventor, which two declarations are then combined into one declaration with a first page of boiler plate, a second page with A's signature, and a second page with B's signature (so that it appears that the declaration was executed with the entire inventive entity appearing in the declaration when it did not). In this case, while the declaration is supplied three times as if the declaration signed by each inventor contained a complete listing of all inventors, since the declaration pages do not properly establish that each inventor was aware of the declaration page containing co-inventors, other than the page each co-inventor actually signed, it cannot be known whether the declaration signed by each inventor contained a complete listing of all inventors.

Accordingly a new oath or declaration in compliance with 37 CFR 1.63 including the entire inventive entity is required. See MPEP 201.03, 605.04 and 37 CFR 1.63.

Specification

6. The disclosure is objected to because of the following informalities:

(a) The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the

specification is Panorex® (see e.g., page 4, line 27).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

(b) In the first sentence, the status of Application 10/778,915 needs to be updated to indicate that it is now abandoned.

(c) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

7. Claims 9 and 22 are objected to as being drawn to the subject matter of a non-elected invention; i.e., claims 9 and 22 are directed in the alternative to the subject matter of the non-elected inventions of Groups I-IV and VI-XXII. These claims are being examined as drawn to the elected invention.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-9, 12 and 17-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1-9, 12 and 17-24 are indefinite because the claims are directed to methods for treating a tumorous disease or colon cancer; yet the claims merely recite the processes of administering a human immunoglobulin specifically binding to the human EpCAM antigen, said immunoglobulin exhibiting a serum half-life of at least 15 days, said method comprising the step of administering said immunoglobulin no more frequently than once every week to a patient. There is no process step that clearly relates back to the purpose or objective of the claimed invention; consequently, the skilled artisan could not determine whether each and every process step considered essential to the practice of the claimed invention has been included in the body of the claim. Thus, in the absence of a correlative step positively relating the whole of the process to its intended use, as recited in the preamble, the claim fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(b) Claims 1-9, 12 and 17-24 are indefinite because the claim recites that an "immunoglobulin exhibiting a serum half-life of at least 15 days". This recitation renders the claims indefinite because the serum half-life can be assayed in multiple different ways in different species, and the half-life will vary greatly depending on the assay system used. Moreover, it is unclear from what time point reference this recital refers because it is unclear if the half-life is measured over at least 15 days or if the immunoglobulin has a half-life of at least 15 days. For example, Oberneder et al (Eur. J. Can., 43:2530-2538, 2006) assays the half life of an antibody, and state 5 different values depending on the assay used and the half-life measured (see e.g, page 2534, right column). Similarly, Gustafson et al (Clin. Exp. Imm., 152:274-279, 2008) evidence that the serum half life of an antibody depends on the route of administration because an antibody can have a different half-life when administered subcutaneously as opposed to intravenously (see e.g, page 277, right column). Notably, the specification does not provide a limiting definition of how to determine a serum half-life because it also identifies different half-lives for an EpCAM antibody at page 19, which depend on

the period of time the half-life is measured over. Accordingly, it is submitted that the metes and bounds of the "immunoglobulin exhibiting a serum half-life of at least 15 days" will vary substantially such that depending on the conditions used to monitor half lives different antibodies would be identified as having a serum half-life of at least 15 days. Therefore, because the metes and bounds of the subject matter that Applicant regards as the invention will vary, these claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite particularity and clarity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(c) In addition, claim 21 is indefinite for the following reason: Claim 21 recites the limitation, "the medicament". There is insufficient antecedent basis for this limitation in the claim because claim 17 does not refer to a medicament. Accordingly, it is submitted that this claim fails to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter.

Therefore, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-9, 12 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In the instant case, the claims are broadly drawn to methods of treating a diverse genus of tumorous diseases in a human patient by administering to said patient a structurally and functionally diverse genus of human immunoglobulins specifically binding to the human EpCAM antigen, said immunoglobulin exhibiting a serum half-life of at least 15 days, said method comprising the step of administering said immunoglobulin no more frequently than once every week (see claim 1) or to methods of treating a diverse genus of tumorous disease comprising administering to a diverse genus of subjects a human immunoglobulin specifically binding to the human EpCAM antigen, said human immunoglobulin exhibiting a serum half-life of at least 15 days comprising administration no more frequently than once every week (claim 17). Claim 12 further recites that the structurally and functionally diverse genus of human immunoglobulins comprise a heavy chain with **an amino acid sequence** as set out in SEQ ID NO:1 and a light chain with **an amino acid sequence** as set out in SEQ ID NO:2.

As a first point, it is noted that claim 17 is broadly drawn to treating a diverse genus of subjects, which e.g., might be from any species other than human; yet the specification only describes humans as expressing a human EpCAM antigen. Notably, other species would not be expected or predicted to express a human EpCAM antigen and therefore, one of skill in the art could not immediately envision, recognize or predict if any other subjects from any other species, could be treated for any tumorous disease by administration of any human immunoglobulin specifically binding to the human EpCAM antigen. Therefore, one of skill in the art would not recognize that Applicant was in possession of methods of treating the broad genus of “subjects" set forth in claim 17.

Secondly, the methods are broadly drawn to administering a diverse genus of "human immunoglobulins specifically binding to the human EpCAM antigen, said immunoglobulin exhibiting a serum half-life of at least 15 days". Notably, the genus of immunoglobulins encompasses a structurally and functionally diverse genus of proteins that includes antibodies, T-cell antigen receptors, MHC molecules and other antibody-like molecules (Elgert et al. Immunology: Understanding the Immune System, 1996, page 59). Furthermore, Elgert defines immunoglobulins, "as a family of globular proteins that comprise antibody molecules and molecules having patterns of molecular structure (antigenic determinants) in common with antibodies," and that "immunoglobulin can be used to refer to any antibody-like molecule". However, in this case, the specification only adequately describes a human antibody comprising a heavy chain with the amino acid sequence of SEQ ID NO:1 and a light chain amino acid sequence of SEQ ID NO:2 that has a terminal half-life calculated after multiple dose administration of 14.74 +/- 4.23, i.e., the maximum half-life disclosed is 19 days (see e.g., page 17-19). While antibodies are a subgenus of the "immunoglobulin" genus, the written description in this case only describes with the requisite particularity required human antibodies that bind human EpCAM because the specification does not envision proteins other than antibodies as "immunoglobulins".

Furthermore, because the claims recite that "a serum half-life of at least 15 days", this broadly, but reasonably encompasses a range of half-lives from 15 days to infinity which could be calculated by any method, but Gustafson et al (Clin. Exp. Imm., 152:274-279, 2008) teach that human IgG has maximal half-lives 3-4 weeks. Accordingly, one of skill in the art would not recognize that Applicant was in possession of the genus of "human immunoglobulins specifically binding to the human EpCAM antigen, said immunoglobulin exhibiting a serum half-life of at least 15 days", because the specification does not identify any particularly identifying structural feature of any human EpCAM antibody which would allow one of skill in the art to immediately envision or recognize human immunoglobulins specifically binding to the human EpCAM antigen which have half-lives from 15 days to infinity.

Furthermore, there is a high degree of unpredictability in assigning a half-life to an antibody and the half life cannot be determined *a priori* because an antibodies half-life depends on numerous factors, including, but not limiter to the assay used to measure the half life. For example, Oberneder et al (Eur. J. Can., 43:2530-2538, 2006) assays the half life of an antibody, and state 5 different values depending on the assay used and the half-life measured (see e.g, page 2534, right column). Similarly, Gustafson et al (Clin. Exp. Imm., 152:274-279, 2008) evidence that the serum half life of an antibody depends on the route of administration because an antibody can have a different half-life when administered subcutaneously as opposed to intravenously (see e.g, page 277, right column). Accordingly, it is submitted that one of skill in the art could not immediately envision or recognize a human immunoglobulin specifically binding to the human EpCAM antigen, said immunoglobulin exhibiting a serum half-life of at least 15 days from any other human immunoglobulin specifically binding to the human EpCAM antigen. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Additionally, while Claim 12 further recites that the structurally and functionally diverse genus of human immunoglobulins specifically binding to the human EpCAM antigen comprising a heavy chain with **an amino acid sequence** as set out in SEQ ID NO:1 and a light chain with **an amino acid sequence** as set out in SEQ ID NO:2, as will be explained in further detail below, the specification only adequately describes a human antibody that specifically binds to the human EpCAM antigen comprising a heavy chain with the amino acid sequence of SEQ ID NO:1 and a light chain amino acid sequence of SEQ ID NO:2.

In this case, because the claim recites "**an** amino acid sequence", as opposed to "the amino acid sequence" the claims are broadly but reasonably being interpreted as directed to a genus of structurally and functionally diverse immunoglobulins that need

only comprise a heavy chain with **an** amino acid sequence as set out in SEQ ID NO:1 and a light chain with **an amino acid sequence** as set out in SEQ ID NO:2. Notably, one of skill in the art readily appreciates that because amino acid sequences provide merely descriptive information about a protein, that an amino acid sequence as set out in SEQ ID NO:2 would include any 2, 3, 4, 5, 6, etc., consecutive amino acids set out in SEQ ID NO:2 because each 2, 3, 4, 5, 6, etc., consecutive amino acids set out in SEQ ID NO:2 is an amino acid sequence. Accordingly, because the immunoglobulins encompassed by this genus could have virtually any structure comprising a heavy chain that merely comprises any 2 consecutive amino acids of SEQ ID NO:1 and a light chain that merely comprises any 2 consecutive amino acids of SEQ ID NO:2, it is apparent that such immunoglobulins do not share any particularly identifying (i.e., substantial) structural feature which would allow one if skill in the art to immediately envision, recognize or distinguish which immunoglobulins comprising a heavy chain with **an** amino acid sequence as set out in SEQ ID NO:1 and a light chain with **an amino acid sequence** as set out in SEQ ID NO:2would specifically bind the human EpCAM antigen.

Notably, it is well-established in the art that there is a high degree of unpredictability in determining the three-dimensional structure and function of a given protein *a priori* given its amino acid sequence.

As evidenced by Jones (Pharmacogenomics Journal, 1:126-134, 2001), protein structure "prediction models are still not capable of producing accurate models in the vast majority of cases" (page 133, 3rd paragraph). Furthermore, Tosatto et al state, "the link between structure and function is still an open question and a matter of debate" (Current Pharmaceutical Design, 12:2067-2086, 2006, page 2075, 1st new paragraph). Therefore, even if the skilled artisan were able to submit a complete list of all the possible immunoglobulins which fall within the scope of the claims, the skilled artisan would not be able to immediately envision, recognize or predict the three-dimensional structure and function of a given immunoglobulin *a priori* based on its amino acid sequence.

For inventions in an unpredictable art, adequate written description of a genus

which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406. Written description of the present application only reasonably conveys possession of a human antibodies that specifically bind to the human EpCAM antigen comprising a heavy chain with the amino acid sequence of SEQ ID NO:1 and a light chain amino acid sequence of SEQ ID NO:2 and not the genus of "human immunoglobulins specifically binding to the human EpCAM antigen comprising a heavy chain with **an amino acid sequence** as set out in SEQ ID NO:1 and a light chain with **an amino acid sequence** as set out in SEQ ID NO:2".

Furthermore, while the prior art human antibodies that specifically binds to the human EpCAM antigen that are cytotoxic to human colon cancer cells (please see art rejection below), as will be discussed in further detail below, there is considerable factual evidence that the ability of a naked antibody (i.e., an antibody not conjugated or otherwise associated with a cytotoxic moiety), and particularly an antibody lacking the Fc effector region (e.g., a scFv), to kill a targeted cell will vary substantially depending upon the epitope (i.e., antigenic determinant) of the antigen.

For example, it is recognized in the art that depending on the epitope bound by an antibody on the antigen expressed by tumor cells that some naked antibodies will inhibit tumor growth while some naked antibodies actually accelerate tumor growth (see e.g., Stancovski et al (PNAS, 88: 8691-8695, 1991 (page 8693, column 1)). While the reason that the naked antibody may be ineffective is not known, Jiang et al. (*J. Biol. Chem.* 2005 Feb 11; **280** (6): 4656-4662), for example, teaches that it is well known that different biological effects are associated with epitope specificity of the antibodies (see entire document, particularly page 4656, column 2). Accordingly, it is also submitted that one of skill in the art would not be able to immediately envision which human immunoglobulins specifically binding to the human EpCAM antigen that have a serum half-life of at least 15 days or which human immunoglobulins specifically binding to the human EpCAM antigen comprising a heavy chain with **an amino acid sequence** as set out in SEQ ID NO:1 and a light chain with **an amino acid sequence** as set out in SEQ ID NO:2 which would be effective in the claimed methods and therefore, one of skill in

the art would not recognize that Applicant was in possession of the claimed methods.

Finally, it is noted that the diverse genus of "tumorous diseases" broadly encompasses benign tumors, yet the specification has not described any benign tumors which might be treated by the disclosed methods. Accordingly, it is submitted that one of skill in the art would not recognize that Applicant was in possession of the claimed methods of treating tumorous diseases.

For these reasons, as a whole, it is submitted that the specification would amount to no more than a mere invitation to the skilled artisan to *discover* the identity of other processes of treating tumorous diseases in patients by administering a structurally and/or functionally diverse genus of human immunoglobulins specifically binding to the human EpCAM antigen that have a serum half-life of at least 15 days or human immunoglobulins specifically binding to the human EpCAM antigen comprising a heavy chain with **an amino acid sequence** as set out in SEQ ID NO:1 and a light chain with **an amino acid sequence** as set out in SEQ ID NO:2 as encompassed by the claims; it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for identifying it.

Once again, given the lack of particularity with which the diverse genus of processes of treating patients or subjects, to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the methods encompassed by this genus; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

12. Claims 1-9, 12 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** methods encompassed by the claims that are suggested by the prior art, **does not reasonably provide enablement for using** the full scope of the claimed processes, such as treating the full

scope of tumorous diseases by administering the full scope of human immunoglobulins specifically binding to the human EpCAM antigen that have a serum half-life of at least 15 days. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In the instant case, the claims are broadly drawn to methods of treating a diverse genus of tumorous diseases in a human patient by administering to said patient a diverse genus of human immunoglobulins specifically binding to the human EpCAM antigen, said immunoglobulin exhibiting a serum half-life of at least 15 days, said method comprising the step of administering said immunoglobulin no more frequently than once every week (see claim 1) or to methods of treating a diverse genus of tumorous disease comprising administering to a diverse genus of subjects a human immunoglobulin specifically binding to the human EpCAM antigen, said human immunoglobulin exhibiting a serum half-life of at least 15 days comprising administration no more frequently than once every week(claim 17). Claim 12 further recites that the structurally and functionally diverse genus of human immunoglobulins comprise a heavy chain with **an amino acid sequence** as set out in SEQ ID NO:1 and a light chain with **an amino acid sequence** as set out in SEQ ID NO:2.

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue experimentation.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

As explained in the above rejection of the claims, as failing to satisfy the written description requirement, because the claims are directed to processes of using a genus of human immunoglobulins specifically binding to the human EpCAM antigen, said human immunoglobulin exhibiting a serum half-life of at least 15 days comprising administration no more frequently than once every week or a genus of human immunoglobulins comprising a heavy chain with **an amino acid sequence** as set out in SEQ ID NO:1 and a light chain with **an amino acid sequence** as set out in SEQ ID NO:2" that have not been described so as to permit the skilled artisan to immediately envision, recognize or distinguish the members of these genera, the skilled artisan could not make these "human immunoglobulins" without undue and/or unreasonable experimentation; and if these "human immunoglobulins" cannot be made without undue and/or unreasonable experimentation, the specification would not reasonably enable the skilled artisan to use the claimed processes without undue experimentation. Notably, e.g., one of skill in the art would be subject to undue experimentation to make the claimed immunoglobulins the half-life of at least 15 days, includes a range of 15 days to infinity, but the specification contains, no specific non-general guidance as to how to make a human EpCAM antibody that has a half-life of over 19 days.

Applicant is reminded reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to

satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Furthermore, as evidenced by Stancovski et al (supra), in the above rejection of the claims as lacking adequate written description, those of skill in the art also recognize the unpredictability of treating patients with tumorous diseases by administering any given antibody that is specific for a human antigen. By way of further explanation, as evidenced by Stancovski et al, antibodies immunoreactive with an antigen expressed on a target cell can accelerate cell proliferation or inhibit cell proliferation. Accordingly, it is submitted that it is highly unpredictable whether any given human EpCAM immunoglobulin can be used in the claimed methods without undue experimentation. For example, one of skill in the art would be subject to undue experimentation to practice the claimed methods to reduce treat tumorous disease if the human EpCAM immunoglobulin administered accelerates cell proliferation. Additionally, where claim 17 broadly encompasses administering human EpCAM immunoglobulins to subject which are not human, because it is highly unpredictable whether any given human EpCAM immunoglobulin can be used to treat any tumorous disease in subjects which are not human, one of skill in the art would be subject to undue experimentation to practice the claimed methods to treat tumorous disease in such subjects.

To further elaborate on the art-recognized unpredictability in treating e.g., patients with cancer, Jain (Scientific American, 271(1):58-65, July 1994) discloses that there are many art known barriers to the delivery of drugs to treat patients with cancer. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the

delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutic molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Furthermore, with particular regard for using antibodies to treat cancer, Dillman, (Annals of Internal Medicine, 111:592-603, 1989) summarizes (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). Also, Weiner (Seminars in Oncology, 26 (4 Suppl 12):41-50, August 1999) provided an overview of monoclonal antibody therapy including some promising activity, however, major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets and insufficient target specificity (see page 43). Therefore, in view of the evidence of the lack of the predictability of the art to which the invention pertains, it is submitted that one of skill in the art would be subject to undue experimentation to practice the claimed methods which comprises administering human EpCAM immunoglobulin with a half life of at least 15 days.

Once again, Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify other processes of treating tumorous diseases that are encompassed by the claims.

In conclusion, upon careful consideration of the factors used to determine

whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 1-9, 12 and 17-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kufer et al (WO 98/46645 A2, 1998), in view of Raum et al (Can. Immunol. Immunother., 50:141-150, 2001) and Naundorf et al (Int. J. Can. 100:101-110, 2002) and as evidenced by Oberneder et al (Eur. J. Can., 42:2530-2538, 2006), Loh et al (J. Nuc. Med., 39:484-489, 1998) and Leyland-Jones (J. Clin. Onc., 221(21):3965-3971, 2003).

The claims are herein drawn to methods of treating colon cancer in a human patient by administering to said patient a human immunoglobulin specifically binding to the human EpCAM antigen, said method comprising the step of administering said immunoglobulin no more frequently than once every week. Notably, while the claims recite that said immunoglobulin exhibits a serum half-life of at least 15 days, since as set forth in the above rejection of the claims under 35 USC 112, second paragraph, the half-life of an antibody varies depending on the assay used, the claims are being broadly, but reasonably interpreted to encompass administering to said patient a human immunoglobulin specifically binding to the human EpCAM antigen. In this case, the half-life of an antibody is an inherent property and, the Office lacks the resources and facilities to determine the half-lives of antibodies disclosed by the prior art. Consequently, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed antibodies are different from the antibodies taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977); and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989). Notably, in this case, Raum et al (Can. Immunol. Immunother., 50:141-150, 2001) teach that human IgG antibodies are known to have long in vivo half lives, while as evidenced by Oberneder et al (Eur. J. Can., 42:2530-2538, 2006) at least one human antibody[1] that specifically binds the human EpCAM antigen disclosed by the prior art references of Kufer et al, Raum et al and Naundorf et al inherently has a terminal half-life measured after multiple dose administration of 15 days (see page 2534, right column).

Dependent claims are further drawn to such methods, further comprising: (a) determining, after a period of at least one week following a respective last administration of said immunoglobulin but prior to a respective next administration of said immunoglobulin, the serum level of said immunoglobulin still present in the blood of

[1] This antibody appears to have been designated H79, HD69, MT201 and adecatumumab in the art. For example, Oberneder evidences that adecutmamab has also been designated MT201 (see abstract). Then Naundorf teaches that the MT201 antibody has also been designated HD69 (see page 102, left column). Finally, Kufer et al teach a antibody designated H79 that comprises a 4.5 heavy chain and a k8 light with heavy chain and light chain variable

said patient, thereby obtaining an intermediate serum level value for said immunoglobulin; (b) comparing said intermediate serum level value for said immunoglobulin with a predetermined serum trough level value for said immunoglobulin; and (c) effecting the respective next administration if the intermediate serum level value for said immunoglobulin is no more than 15%, preferably 10%, most preferably 5% above the serum trough level value or further comprising repeating steps (a) and (b) prior to step (c), or wherein the magnitude of the dose of said human immunoglobulin administered is set such that, at the end of the intervening time between two respective administrations, the amount of said human immunoglobulin persisting in the serum does not drop below the predetermined serum trough level, wherein said administering takes place once every two weeks or wherein said administering takes place less frequently than once every two weeks, wherein said administering takes place once every two weeks and wherein the administered dose of said human immunoglobulin remains unchanged from one administration to the next, wherein said administering takes place less frequently than once every two weeks and wherein both the administered dose of said human immunoglobulin and the frequency of administration remain unchanged from one administration to the next, wherein the magnitude of the initial and all subsequent doses is determined by pharmacokinetic simulation, wherein said administering is intravenous, intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration or wherein said human immunoglobulin comprises an immunoglobulin heavy chain with an amino acid sequence as set out in SEQ ID NO: 1 and an immunoglobulin light chain with an amino acid sequence as set out in SEQ ID NO: 2. Notably, as set forth in the above rejection of the claims under 35 USC 112, first paragraph, because claim 12 recites that the heavy or light chain comprises an amino acid sequence, the claims broadly, but reasonably encompass e.g., any human antibody that comprises 2 consecutive amino acids in a heavy chain and light chain of the recited sequences.

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sequences set forth in figures 6 and 7(see also page 35-37), while Raum et al teach the same sequences for the antibody designated HD69 (see Figure 1 and page 145).

Kufer et al. teach human antibodies that specifically bind to the human EpCAM antigen which also include such antibodies conjugated to radioactive or cytotoxic moieties to said antibody and methods of administering such antibodies to human patients with cancer by intravenous, intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration (see entire document, e.g., abstract and pages 1, 2 12 and 17. Notably, at least one of these human antibodies designated H79, (also known as HD69, MT201 and adecatumumab in the art see footnote) comprises a heavy chain and light chain comprises at least 2 consecutive amino acids of SEQ ID NO:1 and 2 (see Figures 6 and 7). While, Kufer et al. does not point to particular cancers in the genus of cancers to be treated, Kufer et al teaches that a murine monoclonal antibody 17-1A that binds human EpCAM was known to treat human colon or colorectal cancer as well as teaching that the H79 antibody can bind to human colon carcinoma cells (see e.g., 2 and 23). Similarly, Raum et al teach that the murine monoclonal antibody 17-1A that binds human EpCAM was known to treat human colon or colorectal cancer, and that the H79 antibody, now designated HD69 in this reference (see footnote), closely resembles the binding properties of the murine antibody, but that his antibody displays better cytotoxic effector functions (see entire document, e.g., abstract, Table 1 and 146, right column to 147, left column). Then in further characterization of this antibody, now designated MT201 or HD69 in this reference (see footnote), Naundorf et al teach that the antibody is effective in treating a mouse xenograft model of colon cancer derived from the human carcinoma cell line HT-29.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer to human colon cancer patients human antibodies that specifically bind to human EpCAM which are cytotoxic to human colon cancer cells, such as the MT201 antibody or any human antibody that specifically binds to human EpCAM conjugated to a cytotoxic agent as encompassed by the claims by any of the various doses, schedules, and routes of delivery set forth in the claims. Notably, one of skill in the art would have been motivated to administer such antibodies to humans with colon cancer because other EpCAM antibodies target colon cancer cells and treat colon cancer and any human antibody that specifically binds to

human EpCAM which is cytotoxic to human colon cancer cells would be expected to treat colon cancer as well. Furthermore, Raum et al teach that such antibodies would have the advantages of a long in vivo half life and minimal immunogenicity in humans (see e.g., abstract).

In this case, while the prior art cited does not address the specific doses or regimens according to which the human antibodies are administered to colon cancer patients, the claims are not limited to administering any one particular antibody, but rather to a genus of antibodies having equivalent functions; and similarly the prior art teaches multiple different human antibodies that specifically bind to human EpCAM which would be effective to treat colon cancer. In light of such permissible variance, it seems that the doses, schedules, and routes of delivery that are used in practicing the process that is claimed, and the process that is disclosed by the prior art, will vary.

It is a common objective in the art to establish a dose, schedule, and route of delivery that is both safe and effective, so as achieve optimal therapeutic effect and maximal benefit. See *In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." (citations omitted)). See *In re Peterson*, 65 USPQ2d 1379 1382 (CA FC 2003): "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."

For example, as evidenced by Loh et al (J. Nuc. Med., 39:484-489, 1998) (see entire document) and Leyland-Jones (J. Clin. Onc., 221(21):3965-3971, 2003) (see entire document), the pharmacokinetics and pharmacokinetic simulations used to establish a dose, schedule, and route of delivery for therapeutic antibodies are known in the art.

Thus, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have determined the most appropriate doses, schedules, and routes of administration, so as to practice the disclosed process of

treating colon cancer as effectively as possible. One ordinarily skilled in the art at the time the invention was made to do so to optimize the effectiveness of the treatment.

Absent a showing of any unobvious differences, it is therefore submitted that the process disclosed by the prior art would render obvious the process that is claimed.

This position is reasonable since parameters such as dosing, scheduling and routes of delivery, which are used to treat any given condition, may be expected to differ from those that are used most effectively to treat another condition. In general, these parameters that are used most efficaciously can only be determined in clinical trials designed to determine those parameters. The Office, however, does not have the facilities or resources for conducting clinical trials to determine if therapeutic agents are used effectively in particular regimens, as in accordance with the claims; so, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed process is different than that taught and/or suggested by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

15. No claims are allowed.

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Roovers et al (Can. Immunol. Immunther., 50:51-59, 2001) teach human antibodies which bind to human EpCAM antigen that bind to colon cancer cells.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
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/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
December 20, 2008